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By Facsimile and Regular Mail

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD WC-05
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Ninth Annual Report on Carcinogens

Dear Dr. Jameson:

The Fertilizer Institute (TFI), on behalf of its member companies, submits these comments in response to a July 11, 1997 National Toxicology Program (NTP or Program) notice in the Federal Register soliciting comments on NTP's list of substances, mixtures and exposure circumstances for possible inclusion in the Ninth Annual Report on Carcinogens (62 Fed. Reg. 37,272).

Statement of Interest

TFI is a voluntary, non-profit trade association of the fertilizer industry. TFI's nearly 250 member companies manufacture over 90 percent of the domestically produced fertilizer. TFI's membership includes producers, manufacturers, distributors, transporters and retail farm suppliers of fertilizer and fertilizer materials. In the production of phosphoric acid-based fertilizers, large amounts of sulfuric acid are produced and utilized by TFI's members. Thus, TFI and its member companies have a vital interest in any effort by NTP to evaluate the carcinogenicity of sulfuric acid mist.

Description of the Production Process

Fertilizer manufacturers utilize the wet process to produce phosphoric acid. It is estimated that 95 percent of the commercial grade wet-process phosphoric acid is used to produce fertilizers and animal feed, with a small portion used as a feedstock in chemical processing operations. The wet process for the production of phosphoric acid includes three basic operations: digestion; filtration; and concentration. Sulfuric acid is relevant to the first operation, digestion.

As part of the digestion operation, beneficiated phosphate rock is added to a recirculating phosphoric acid stream, generating calcium phosphate. Sulfuric acid is then added to the solution to chemically precipitate calcium sulfate solid (phosphogypsum) and leave phosphoric acid in solution. TFI's members captively produce sulfuric acid at their phosphoric acid production facilities. In fact, 71 percent of the sulfuric acid in the United States is produced captively for use in phosphoric acid production. Thus, any evaluation of the carcinogenicity of sulfuric acid, in any form, is of import to TFI's members.1/

Discussion

TFI offers the following preliminary comments on NTP's notice of intent to evaluate sulfuric acid mist for inclusion in the Ninth Annual Report on Carcinogens.

I. NTP Should Undertake A Rigorous Review of the Studies Identified as Relevant to Evaluating Sulfuric Acid Mist

TFI urges NTP to conduct a critical, independent review of the studies which NTP ultimately concludes are applicable to sulfuric acid mist, instead of merely adopting the conclusions reached in those studies. TFI believes that NTP has adopted a contrary approach based on a statement contained in NTP's Seventh Annual Report on Carcinogens (1994), the Program's most recent report. In this Report, NTP "reminds" the public that the Report:

> is a condensation of large amounts of data and conclusions made by bodies which peer review the data submitted as evidence about cancer and its relation to specific exposures. As such, the Seventh Annual Report on Carcinogens must be less detailed about the actual tests and their drawbacks. The original monographs on each listing are given in the references, and the reader is advised to turn to these for the specific arguments, both pro and con, which went into the listing decision.

Seventh Annual Report on Carcinogens at 4.

TFI urges NTP to utilize its scientific expertise to conduct its own, independent assessment of the "pros and cons" associated with each sulfuric acid mist study. Specifically, NTP should critically evaluate the confounding factors for each study, as well as inconsistencies between one study and

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1/ The remaining two operations, filtration and concentration, do not entail sulfuric acid use.

another. Unless NTP undertakes such a thorough, in depth, review of each study, it will not be properly evaluating a chemical for known, or reasonably expected, human carcinogenicity.

II. NTP Should Promulgate a Definition of "A Significant Number of Persons" For Purposes of the Annual Report on Carcinogens

TFI requests that NTP promulgate a definition of "a significant number of persons" for purposes of its carcinogenicity listing prior to evaluating the 14 substances for inclusion in the Ninth Annual Report on Carcinogens. As NTP is aware, the Public Health Service Act, Section 262,2/ provides NTP, through delegation from the Secretary of the Department of Health and Human Services (HHS), with the statutory authority to publish a report on carcinogenicity. Specifically, Section 262 requires HHS to publish a biennial report which contains:

> (A) a list of all substances --
>
> (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens, and
>
> (ii) to which a significant number of persons residing in the United States are exposed;
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> * * * *

Under this statutory listing scheme, NTP must first ascertain whether a substance is either (1) known, or (2) reasonably anticipated, to be a carcinogen. NTP makes this determination through reviewing studies on the substance at issue and accepting public comments on the substance. As reflected in the attachment which NTP provided to TFI, NTP has developed a very elaborate review protocol for assessing a substance's carcinogenicity. However, even if a substance satisfies the "carcinogenicity" test, it still must pass the "significant exposure" test before it may be listed in the report.

Under Section 262, a substance, once it is concluded that it is a known, or reasonably anticipated to be, carcinogen, cannot be listed unless NTP also concludes that "a significant number of persons residing in the United States are exposed [to it]." Although NTP appears to have devoted considerable resources to establishing a system to implement the first part of the listing decision (i.e., carcinogenicity), NTP has not, to the best of TFI's knowledge, devoted resources to determining how to

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2/ This section is codified at 42 U.S.C. § 241.

evaluate the second part of the listing decision (i.e., a significant number of persons exposed to the substance). Because this part of the listing analysis is as crucial as the first part, NTP should not engage in listing determinations without properly establishing a clear definition of the number of persons required to be exposed to the substance for listing purposes.

Also, as part of NTP's efforts to better define the second part of the listing criteria, NTP should focus on the word "exposed." As previously stated, the second part of the listing analysis requires that "a significant number of persons residing in the United States [be] exposed" to the known, or reasonably anticipated to be, carcinogen. NTP should define what is meant by the word "exposed." In other words, is it exposure at a certain concentration? Or rather, is it exposure at any concentration? TFI believes that NTP should define "exposed" in terms of a dose (i.e., exposure at a given concentration for a designated period of time). To develop this definition, NTP should conduct rigorous risk assessments to determine the proper safe exposure for an identified carcinogen.

Because NTP's listing of a substance as a carcinogen, or suspected carcinogen, triggers other regulatory requirements at the federal and state level, TFI requests that any effort to define what is meant by a "significant number" and "exposed" be addressed in the context of notice and comment rulemaking pursuant to the Administrative Procedure Act.

An example of a regulatory requirement triggered by NTP's identification of a substance as a carcinogen, or suspected carcinogen, is the U.S. Occupational Safety and Health Administration's (OSHA's) Hazard Communication (HAZCOM) Standard (29 C.F.R. § 1910.1200). Under this Standard, chemical manufacturers and importers are required to assess the hazards of the chemicals which they produce or import to determine if they are "hazardous chemicals." If the chemical is a hazardous chemical, the manufacturer or importer must prepare a material safety data sheet for the chemical and ensure that any containers leaving the work place are properly labeled. In addition, employee's exposed to the chemical in the work place must be trained in the proper handling of the chemical. A "hazardous chemical" is defined under the Standard as a chemical which is a "physical" hazard or a "chemical" hazard. A chemical hazard includes those chemicals that are "listed as a carcinogen or potential carcinogen in the Annual Report on Carcinogens published by the National Toxicology Program (NTP)." 29 C.F.R. § 1910.1200, App. A. Thus, a listing by NTP in the Annual Report on Carcinogens triggers compliance with OSHA's HAZCOM Standard. Because of the regulatory implications of an NTP listing, such as applicability of OSHA's HAZCOM Standard, NTP should provide the public with the opportunity to assist NTP in developing a working protocol to list chemicals in its Annual Report on Carcinogens.

III. Potential Listing of Sulfuric Acid Mist

In its description of the procedures for evaluating chemicals for inclusion in the Seventh Annual Report on Carcinogens, NTP states that the "strongest evidence for relationships between exposure to any given chemical and cancer in humans comes from carefully conducted epidemiological

studies." Seventh Annual Report on Carcinogens at 4. TFI agrees with this conclusion. An epidemiological study of mortality in relation to work experience in the Florida phosphate industry was conducted in the 1980's and updated in 1995. The study, which included over 24,000 workers employed in the industry between 1949 and 1978, found no evidence of causal associations of lung cancer or of general mortality with specific exposures, including acid mist. It is this type of epidemiological data that NTP should rely upon when it evaluates sulfuric acid mist for inclusion in the Ninth Annual Report on Carcinogens.

In evaluating the potential listing of sulfuric acid mist, NTP will certainly consider the work conducted by the International Agency for Research on Cancer (IARC). In 1992, IARC issued a monograph identifying strong inorganic acid mists containing sulfuric acid as carcinogenic. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans at 106 (Vol. 54, 1992). The studies relied upon by IARC to reach its conclusion concerning strong inorganic mists failed to adequately consider the confounding effects of significant elements, such as smoking and alcohol consumption. Also, IARC failed to adequately extrapolate from experimental data to human exposure.

TFI appreciates the opportunity to submit these comments and will be commenting on future NTP notices in the Federal Register concerning the evaluation of sulfuric acid mist for inclusion in the Ninth Annual Report on Carcinogens. In the meantime, if there are any questions regarding these comments, please feel free to contact Don Casey of TFI at (202) 608-5909.

Sincerely yours,

Gary D. Myers
President

Att.

REPORT ON CARCINOGENS LISTING/DELISTING PROCEDURES

Petitions for listing or delisting an agent, substance or mixture in the Report on Carcinogens (The Report) should be submitted to the National Toxicology Program[1]. Petitions must contain a rationale for listing or delisting as either a "known human carcinogen" or a "reasonably anticipated human carcinogen". Appropriate background information and relevant data (e.g. journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories, etc.) which support a petition should be provided or referenced.

An agent, substance or mixture petitioned for listing or delisting will be announced in the Federal Register, trade journals and NTP newsletters to solicit public comment. The original petition and all comments received will be evaluated by an NIEHS/NTP Review Group (RG1), composed of scientists from the NIEHS/NTP, to determine if the information provided is sufficient to merit further consideration. If it is determined the petition warrants formal consideration, the NTP may initiate an independent search of the literature and prepare a draft review document for the substance under consideration. Draft documents will be prepared according to the following general format:

1.0 Introduction
- 1.1 Chemical Information
  - synonyms, trade names, CAS#'s, molecular formula, molecular structure, etc.
- 1.2 Physical-Chemical Properties
- 1.3 Identification of Structural Analogs

2.0 Exposure Assessment
- 2.1 Production
- 2.2 Use
- 2.3 Environmental Exposure
  - environmental occurrence, environmental release, drinking water and food content, consumer products, occupational exposures, biomarkers of exposure
- 2.4 Regulations
  - Occupational Exposure Limits (standards and criteria), "other" standards and criteria

3.0 Human Studies
- 3.1 Epidemiology Studies
  - occupational studies, clinical trials, consumer exposure, other "non-occupational" exposures
- 3.2 Laboratory Studies
  - controlled exposures

3.3 Poisonings
case reports, accidents, symptoms and clinical signs

4.0 Animal Carcinogenicity Studies
subdivided by species

5.0 Genotoxicity

6.0 Mechanistic and Other Relevant Studies

Data used in the preparation of Sections 3 through 6 of the draft document must come from publicly available, peer reviewed sources.

If it is determined that the petition contains insufficient information to warrant consideration by the NTP, it will be returned to the original petitioner who will be invited to resubmit the petition with additional justification, which may include new data, exposure information, etc. A notice, stating the action taken for a petitioned substance found to contain insufficient justification for consideration, will be published in the Federal Register, trade journals and NTP newsletters, and included in subsequent editions of the Report with the reason(s) why it was not considered further. This decision will also be forwarded to the NTP Executive Committee and Board of Scientific Counselors.

FORMAL REVIEW STEPS

The following describes the review process for petitions that are considered by the NTP for listing in or delisting from the Report on Carcinogens.

NIEHS/NTP Review Group (RG1)

The original petition and all public comments received in response to a petition will be reviewed by RG1. Assignment of a primary and secondary reviewer will be made upon receipt of a petition. Reviewers will lead discussions concerning the adequacy of the petition. If the petition warrants formal consideration a search of pertinent data bases will be performed and available citations will be reviewed by the primary reviewer. The primary reviewer will identify the relevant articles. After consultation with the secondary reviewer, the identified literature will be obtained and a draft summary of all available information from the original petition and the literature search will be prepared. The primary and secondary reviewers will examine the petition, the literature citations and the draft document for completeness and adequacy. The draft document will be revised if necessary and presented by the primary reviewer to the RG1. Public comments received in response to announcements of petitions will also be considered. The RG1 will make a formal recommendation for those petitions determined to contain sufficient information for listing or delisting in the Report. The petition then continues through the review process.

Petitions reviewed by RG1 for which sufficient information could not be obtained will not proceed further. The other Report review groups, as well as the NTP Executive Committee, will be informed of this action. The original petitioner will be notified of the RG1 action and invited to resubmit the petition with additional justification. All

petitioned agents, substances, or mixtures reviewed by RG1 but not selected for listing or delisting will be included in the subsequent edition of the Report with the reason(s) why they were not considered further.

NTP Executive Committee's Working Group for the Report on Carcinogens (RG2).

The second review phase of petitions will be done by the NTP Executive Committee's Working Group for the Report on Carcinogens (RG2). RG2 is a Governmental interagency group that assesses whether relevant information on the petitioned agent, substance, or mixture is available and sufficient for listing in or delisting from the Report. A reviewer for each petition will be assigned from the RG2 who will be responsible for reviewing the draft document and for leading the Working Group's discussion of the petition. Public comments received in response to announcements of petitions will also be considered by RG2 during the review. Upon completion of its review, RG2 will provide comments and recommendations for any changes and/or additions to the draft document and also make its recommendation for listing or delisting. The petition then continues through the review process.

Board of Scientific Counselors REPORT Subcommittee (External Peer Review).

The third review phase for petitions will be performed by a subcommittee of the NTP Board of Scientific Counselors. This subcommittee serves as another independent peer review group that assesses whether the relevant information available is sufficient for listing in or delisting. The NTP Board Report Subcommittee will review petitions in a public meeting. Prior to public review, a notice will be published in the Federal Register, trade journals, and NTP newsletters, soliciting public comment. The notice will also invite interested groups or individuals to submit written comments and/or to address the NTP Board Report Subcommittee during the review meeting. Reviewers for each petition will be assigned from the NTP Board Report Subcommittee who will be responsible for reviewing the draft document and leading the subcommittee's discussion of the petition. Upon completion of its review, NTP Board Report Subcommittee will provide comments and recommendations for any changes and/or additions to the draft document and also make its formal recommendation for listing or delisting the petitioned agent, substance, or mixture.

Upon completion of the reviews by RG1, RG2, and NTP Board Report Subcommittee, those petitioned agents, substances, or mixtures which are recommended for listing in or delisting from the Report, will be published in the Federal Register, trade journals and NTP newsletter publications, and public comment and input on the recommendations will be solicited.

NTP Executive Committee

The independent recommendations of RG1, RG2, and NTP Board Report Subcommittee and all public comment will be presented to the NTP Executive Committee[2] for review and comment.

NTP Director

The Director, NTP receives the four independent recommendations from RG1, RG2, NTP Board Report Subcommittee, and the NTP Executive Committee and makes the final decision to submit the Report to the Office of the Secretary, DHHS. Upon review and approval by the Secretary, DHHS and submission to Congress, a notice of the Report publication, indicating all newly listed or delisted agents, substances, or mixtures will be published in the Federal Register, trade journals and NTP newsletter publications.

[1] National Toxicology Program, Report on Carcinogens
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[2] Agencies represented on the NTP Executive Committee include:
Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Center for Toxicological Research (NCTR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Cancer Institute (NCI), National Library of Medicine (NLM), and National Institute of Environmental Health Sciences/NTP (NIEHS/NTP)